REMARKS

Claim 7, 10, 12, 14-18, 20, 22-25 and 30-38 are currently pending. Claims 12, 14, 22, 23 and 32-38 have been withdrawn from consideration. However as noted in the previous response, Applicant notes that in the event that claim 7 is allowed, claims 12, 14 22, 23 and 32-38 would be subject to rejoinder in view of MPEP 821.04(b).

Claims 7 and 24 have been amended to more distinctly claim that which Applicant regards as the invention. Specifically claim 7 has been amended to replace commas with semicolons to more clearly delineate phrases. Furthermore, claims 7 and 24 have been amended to clarify that a sequence segment between nucleotides 41738-9502 of SEQ ID NO:4 encodes human mouse double minute 2 homolog depicted in SEQ ID NO:2. Further, claim 7 has been amended to clarify that the 5'-noncoding region is between nucleotides 51039-41739 of SEQ ID NO:4 and the 3'-non-coding region is between nucleotides 9503-1 of SEQ ID NO:4. Claim 24 has also been amended to correct an editorial error to insert "a" before contiguous intron-exon region.

Even though this amendment is submitted after a final rejection has been issued, Applicant respectfully requests that the amendment be entered. This amendment will put the claims at the least in better condition for Appeal and in Applicant's view for allowance.

1. The Rejection Under 35 USC §112, First Paragraph

Claims 7, 10, 15-18, 20, 24, 25, 30 and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Office Action specifically states:

> Claim 7, with dependent claims 10, 15-18, 20, 30 and 31, has been amended on March 3, 2005 and August 29, 2005 and claim 24, with dependent claim 25, was added on March 3, 2005 and amended on August 29, 2005 to recite "wherein a sequence segment comprising 41738-9502 of SEQ ID NO: 4 encodes human mouse double minute 2 homolog depicted in SEQ ID NO:2, ... a region comprising a dinucleotide of the following group: 41739-41738, ... and/or 9504-9503" (lines 12-15 of claim 7). Applicant does not indicate and the examiner is unable to locate adequate support in the specification for such positions/ranges in SEQ ID NO: 4.

It is also noted that claim 7, starting from line 17, indicate ***nucleotide ranges*** for various binding sites for huMDM2, location in SEQ ID NO: 4 (claims filed 9/14/2008), pages 2-8. However, there is no basis for these nucleotide ranges (For Example: AP1_C: 36-46, 2876-2886; AP4_Q5: 7944-7980 (starting on page 2 of claims filed 9/14/2008..... to ....nucleotides ranges for the binding sites on pages 3, 4, 5, 6, 7 &8).....

Thus there is no indication that the specific segments or ranges were within the scope of the invention as conceived by Applicants at the time the application was filed....

....Applicants arguments are considered but not found to be persuasive because the specification as originally filed does not teach the specific ranges that related to the specific dinucleotide ranges or the specific *'exon/intron'* organization in term of the specific nucleotide range(s).

Based upon the teachings of Table 2, on page 10, wherein Exon 1 begins at nucleotide 40646 of SEQ ID NO: 4 and the stop codon terminates at nucleotide 10091 of SEQ ID NO: 4. However is it not clear that nucleotides 41738-9502 of SEQ ID NO: 4 would constitute a sequence segment that encodes human mouse double minute 2 homolog protein. Similarly, the region comprising a dinucleotide i.e., nucleotides '41739-41738', does not have no basis in the instant specification.

Before, responding to each of the points made, Applicant wishes to make the following comments. First, in response to the comment made in the Office Action that according to Table 2, Exon 1 begins at nucleotide 40646, Applicant notes that according to Table 2, Exon 1 actually begins at nucleotide 40726. Second, the Examiner had referenced a statement made by Applicant in previous response "A region encompassing the dinucleotide 41739-41738 would be within the 3'noncoding region and would thus constitute a fragment containing a 3'non-coding region". Applicant wishes to clarify that the dinucleotide 41739-41738 is at the 5' end of SEQ ID NO:2.

In response to the rejection under 35 USC §112, first paragraph, Applicant asserts that there is more than adequate support in the specification for claims 7, 10, 15-18, 20, 30 and 31 and in particular, the sequence segment 41738-9502, the ***nucleotide ranges*** for various binding sites for huMDM2, location in SEQ ID NO: 4, specific ranges that relate to the specific dinucleotide ranges or the specific *'exon/intron'* organization in terms of the specific nucleotide range(s) and in particular, the region comprising a dinucleotide i.e., nucleotides '41739-41738'.

First, there is support for the sequence segment 41738-9502. As noted above, Table 2 indicates that Exon 1 begins at nucleotide 40726. It is further indicated that the stop codon is at nucleotides 10089-10091 of SEQ ID NO:4. However, there are further nucleotide sequences set forth in SEQ ID NO:4, nucleotides 51039-40727. Claim 7 has been amended to recite that a contiguous sequence segment between nucleotides 41738-9502 of SEQ ID NO:4 encodes human mouse double minute 2 homolog depicted in SEQ ID NO:2 and clarifies that any contiguous sequence segment between nucleotides 41738-9502 that encodes human mouse double minute 2 homolog depicted in SEQ ID NO:2 is encompassed. Table 2 covers nucleotides 40726-10089 which sets forth "Exon/Intron Organization of the Human Mouse Double Minute 2 Homolog Gene... in SEQ ID NO:4, 51039 Base Pairs; Nucleotides 99541-150570 in the Genomic Clone of Accession No. AC025423". Thus, there is support for the segment 41738-9502.

There is also support for the ***nucleotide ranges*** for various binding sites for huMDM2, located in SEQ ID NO: 4. The various binding sites are set forth in Table 3. Further, paragraph bridging pages 9 and 10 states:

> The invention is further directed to polynucleotide fragments containing or hybridizing to noncoding regions of the human carboxypeptidase M or human mouse double minute 2 homolog genes. These include but are not limited to an expression control element, an intron, a 5'- non-coding region, a 3'- non-coding region and splice junctions (see Tables 1-2, as well as transcription factor binding sites (see Table 3). The polynucleotide fragments may be a short polynucleotide fragment which is between about 20 nucleotides to about 50 nucleotides in length. Such shorter fragments may be useful for diagnostic purposes. Such short polynucleotide fragments are also preferred with respect to polynucleotides containing or hybridizing to polynucleotides containing splice junctions. Alternatively larger fragments, e.g., of about 50, 150, 500, 600, 2000 or about 5000 nucleotides in length may be used.

Further, there is support for the recitation "a region comprising a dinucleotide of the following group: 41739-41738". Specifically, page 5, lines 8-10 states:

> The genes encoding human carboxypeptidase M and the human mouse double minute 2 homolog are disposed in the chromosome 12 genomic clone of accession number AC025423, 150579 base pairs, at, respectively, nucleotides 1 – 99860 and 99541 – 150579.

The MDM2 gene is set forth in the Sequence Listing as SEQ ID NO:2 (nucleotides 1-51039 of SEQ ID NO:3). Further, as noted above, the paragraph bridging pages 9 and 10 indicates that fragments are encompassed as well. Thus, the region comprising a dinucleotide i.e., nucleotides '41739-41738', does not have no basis in the instant specification.

In conclusion, there is adequate support for the phrase in claim 7 "wherein a contiguous sequence segment between 41738-9502 of SEQ ID NO:4 that encodes human mouse double minute 2 homolog depicted in SEQ ID NO:2, ... a region comprising a dinucleotide of the following group: 41739-41738, ... ". Further, there is adequate support for claim 24 directed to an isolated nucleic acid molecule 20-5000 nucleotides in length consisting of a reverse or forward strand of a contiguous exon-intron region or intron-exon region between nucleotides 41738-9502 of SEQ ID NO:4 and claim 25 directed to "an isolated nucleic acid molecule 20-5000 nucleotides in length comprising nucleotides 41739-41738....". Further, claims 10, 15-18, 20, 24, 25, 30 and 31 ultimately depend from claim 7. Thus, arguments made with respect to claim 7 would apply to these claims as well. Therefore, Applicant respectfully request that the rejection under 35 USC 112, written description be withdrawn.

2. The Rejection Under 35 USC 103

Claims 7, 10, 15-18, 20, 24, 25, 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muzny et al. in view of Vogelstein et al. The Office Action states:

> Applicant argues "In Appellant's view, it would not have been obvious to combine the disclosure of Muzny and Vogelstein given that there was no suggestion to do so. Muzny merely contains just a small portion of chromosome 12 DNA. Chromosome 12 is about 130 million base pairs long and is believed to contain several hundred genes (by analysis after 2001 and after the Applicant discovered the human MDM2 homologue gene). Muzny et al knew that clone AC025423 (from 1VII-611 02) was from chromosome 12 but there is no evidence in the NCBI report of a sub-assignment to the p- or q-arm. Further, there is no evidence that Muzny knew whether the clone did or did not contain one or more genes and particularly whether it contained the gene encoded by SEQ ID NO: 4. As will be discussed in further detail below, the MDM2 cDNA constitutes just 1.6% of the clone disclosed by Muzny. Undue experimentation would have been required not only to locate the MDM2 gene but also identify exon-intron junctions" (Supplemental Appeal Brief of 3/2/08, page 11).

Applicant further argues Second, Appellant asserts that there would not be a reasonable expectation of success of obtaining the claimed non-coding sequences of SEQ ID NO: 4 in view of the cited references. Vogelstein placed the human MDM2 homologue gene at 12q12-14. As noted above, there was actually a previous disclosure stating that the MDM2 was located between 12q14.3-15 (see, for example, Andersen et al., 1996, Mammalian Genome 7:780-783 and Bureau, 1995, Genomics 28: 109-112, submitted and disclosed in previous response attached hereto as Exhibit 1). However, given the conflicting locations published as of the priority, one of ordinary skill in the art would not have known which location was actually correct" (Brief, page 14).

This is not agreed with because the actual location does not matter as long as it is a part of the Muzny sequence, which it is. Applicant did not need to separate the Muzny sequence into the fragments containing different arms of chromosome 12. In fact, Applicant did not isolate the fragment 12q12-14 or 12q14.3-15. He run cDNA against the genomic DNA disclosed by Muzny and found the location of the gene where it was. This experiment was performed according to the knowledge and the state of the art as evidenced by Watson et al. Watson et al. teach that "once the first genes were cloned, introns were identified by comparing the cloned genomic DNA with the corresponding cloned cDNA" ("Recombinant DNA", page 137, 2nd column, form PTO892 mailed 4/16/07). Applicant's argument would be convincing if the exact location would need to be known before the comparison of the genomic and the cDNA is made. This is not the case because the work is done on the genomic DNA that is known without fragmentation thereof. Applicants further argues that "Watson would not apply in this case since in Watson, the genes themselves were actually cloned" (ibid, page 18, last sentence). This is not persuasive because Muzny provided the piece of the genomic DNA containing the requisite gene. Having the cDNA, it does not require undue experimentation to identify the fragment of the genomic DNA corresponding to the gene and exon-intron locations within said gene.

The second type of Applicant's arguments concerns with the fact that the cDNA constitutes only 1.6% of the genomic DNA. While the large quantity of the experimentation may be involved, it is not undue because sufficient guidance and knowledge are provided by the art.

Applicant again respectfully traverses the rejection. First, Applicant disagrees with the assertion made in the Office Action that the actual location does not matter as long as it is a part

of the Muzny sequence. Applicant notes that there were two disclosures in the art regarding the possible location of the Muzny sequence, Vogelstein and Andersen. One of skill in the art would not have known where to look. Further, as noted above, even assuming *arguendo* that there was a motivation to combine the two references, one of ordinary skill in the art would not have obtained the claimed sequences. Specifically, Applicant notes that Vogelstein placed the human MDM2 homolog gene at 12q12-14. After publication of Vogelstein, the MDM2 homolog gene was found to be located several kilobases away at 12q15. Thus, Applicant would have looked in the wrong place and would not have obtained the claimed sequence. Therefore, in this instance, the location is particularly pertinent.

Applicant disagrees with the assertion made

> Watson et al. teach that "once the first genes were cloned, introns were identified by comparing the cloned genomic DNA with the corresponding cloned cDNA….. Applicant's argument would be convincing if the exact location would need to be known before the comparison of the genomic and the cDNA is made. This is not the case because the work is done on the genomic DNA that is known without fragmentation thereof. Applicants further argues that "Watson would not apply in this case since in Watson, the genes themselves were actually cloned" (ibid, page 18, last sentence). This is not persuasive because Muzny provided the piece of the genomic DNA containing the requisite gene.

In response, Applicant wishes to point out that until Applicant's discovery, the structure of the MDM2 gene was not actually known. *Contra* to the assertions made above, Muzny merely provided a genomic clone that was 150,579 nucleotides in length. The MDM2 gene was contained within this sequence but there was no indication in Muzny as to where it might be. Further, there was no indication regarding the number of possible introns and exons and where they may actually be located. In Watson, the structure of the gene was actually known and the mRNA was known. Thus, one could deduce the gene sequence and its various coding and noncoding regions. Here, only a large genomic clone had previously been disclosed with the MDM2 gene present somewhere. Considerably more experimentation would be required to determine the various coding and noncoding regions and further even to determine the location and isolate the MDM2 gene. As previously stated, one of ordinary skill in the art reading Watson et al. would conclude that it would be necessary to do electron microscopy of genomic DNA and mRNA hybrids **before** comparing cDNA and genomic DNA in order to have an idea of the

location of the intron-exon boundaries. Simply comparing cDNA and genomic DNA given the teaching of Watson would not be sufficient. Thus, it is still Applicant's view that Watson would be of limited relevance.

Applicant disagrees with the position taken that it would not be undue experimentation to obtain the fragments of the present invention. In order to actually obtain the fragment of the present invention, it would be necessary for Applicant to first to determine the sequence of the MDM2 gene. The clone AC025423 is 150,579 nucleotides in length. The cDNA sequence only contains 2372 nucleotides (1.6% of AC025423). However, one of ordinary skill in the art would not know where or how these 2372 nucleotides are interspersed within the AC025423 clone or if indeed it is even present. No teachings are provided as to the structure of the MDM2 gene itself: number and size of exons, number and size of introns, locations of exons and introns and number and size of 5' and 3' untranslated regions. The possibilities are close to infinite. Further, there was no teaching regarding the size of the MDM2 gene. Thus there would not be a reasonable expectation of success of obtaining the claimed sequences given that the isolation and identification of the claimed sequences constitutes undue experimentation.

In view of the above arguments, Applicant asserts that the rejections under 35 USC 103 have been overcome. Therefore, Applicant respectfully requests that the rejections be withdrawn.

3. Conclusion

In view of the foregoing, Applicant assert that the claims are now in condition for allowance. Early action to that end is respectfully requested. The Examiner is invited to contact the undersigned at (914) 712-0093 if she has any questions.

Respectfully submitted,

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